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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/626,242	09/27/2000	Leo G. Frenken	PM-271592/T3	8145

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EXAMINER	
PONNALURI, PADMASHRI	
ART UNIT	**PAPER NUMBER**
1639	18

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/626,242	Frenken et al
Examiner	**Art Unit**
Padmashri Ponnaluri	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 28, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The amendment and response filed on 7/28/03 has been fully considered and entered into the application.

2. Claims 5-7 have been canceled and claims 1 and 4 have been amended.

Claims 1-4 are currently pending and are being examined in this application.

3. The abstract filed on 7/28/03 has been considered and entered into the application.

4. The objection to claim 4 has been withdrawn in view of the amendment to the claim.

5. The rejection of claims under 35 U. S. C. , 112 second paragraph as indefinite set forth in the previous office action have been withdrawn in view of the amendment to the claims.

6. The obviousness-type double patenting rejections set forth in the previous office action has been withdrawn in view of the terminal disclaimer filed on 7/28/03.

Maintained Rejections

7. The rejection of claims 1-4 under 35 U.S.C. 102(a) as being anticipated by US Patent 5,800,988 (Casterman et al , filed on June 6, 1995) has been maintained for the reasons of record set forth in the previous office action mailed on 1/27/03.

8. The rejection of claims 1-4 under 35 U.S.C. 102(b) as being anticipated by EP 584421 A1, published March 02, 1994 has been maintained for the reasons of record set forth in the previous office action mailed on 1/27/03.

9. The rejection of claims 1-4 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ghahroudi et al (FEBS Letters, 414 (1997) 521-526) has been maintained for the reasons of record set forth in the previous office action mailed on 1/27/03.

Response to Arguments

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by US Patent 5,800,988 (Casterman et al , filed on June 6, 1995).

The instant claims briefly recite an expression library comprising a repertoire of nucleic acid sequences, each nucleic acid sequence encoding a part of variable domain of a heavy chain derived from an immunoglobulin naturally devoid of light chains.

Casterman et al disclose immunoglobulins devoid of light chains (refers to 'naturally devoid of light chains' of the instant claims). The reference discloses that the disclosed immunoglobulins comprise two heavy polypeptide chains sufficient for formation of a complete antigen binding site (i.e., see column 2, lines 32-33). The reference discloses that the disclosed immunoglobulins are further characterized by the fact that they are the product of the expression in a prokaryotic or in a eukaryotic host cell of DNA or of cDNA having sequence of an immunoglobulin devoid of light chains as obtainable from lymphocytes or other cells of camelids (i.e., see column 2, lines 35-40) (refers to the instant

claims 1-4). The reference discloses cDNA libraries to isolate nucleic acid sequences coding for immunoglobulins of the invention (i.e., see column 11, lines 10-11). The reference discloses that the nucleic acid sequences of the disclosed immunoglobulins are used for the preparation of recombinant vectors and the expression of these sequences contained in the vectors by host cells (i.e., see column 11, lines 14-15). The reference discloses V_{HH} (variable heavy chain of immunoglobulin devoid of light chain) repertoire (refers to the repertoire of nucleic acid sequences of the instant claims) using DNA derived from an arbitrarily chosen tissue or cell type or V_{HH} repertoire using DNA obtained from B lymphocytes. The reference discloses in column 12, a cDNA library composed of nucleotide sequences coding for a heavy chain immunoglobulin by treating a sample containing lymphoid cells, especially from peripheral lymphocytes, spleen cells, lymph nodes or other lymphoid tissue from a healthy animal, especially selected from Camelids. The reference discloses that the preparation of the antibodies can also be performed without a previous immunization of Camelids (see column 14, lines 15-16) (refers to the 'non-immunized source' of the instant claims). Thus the reference clearly anticipates the claimed invention.

11. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 584421 A1, published March 02, 1994.

The instant claims briefly recite an expression library comprising a repertoire of nucleic acid sequences, each nucleic acid sequence encoding a part of variable domain of a heavy chain derived from an immunoglobulin naturally devoid of light chains.

EP 584421 A1 discloses immunoglobulins devoid of light chains. The immunoglobulins disclosed by the reference comprise two heavy chain polypeptide chains sufficient for the formation of a complete antigen binding site or several antigen binding site and devoid light polypeptide chains (refers to 'naturally devoid of light chains' of the instant claims) (i.e., see last paragraph in page 2). The reference discloses that the immunoglobulins can be isolated from animals, and are called 'heavy chain immunoglobulins. The reference discloses that the heavy chain immunoglobulins of the invention are secreted in blood of camelids (i.e., see page 3, lines 45). And the reference discloses methods for

obtaining nucleotide sequences coding for all or part of the immunoglobulins, and the nucleotide sequences can be used for the preparation of recombinant vectors and the expression of these sequences contained in the vectors by host cells (refers to the instant claim 1) (i.e., see page 7). The reference discloses that V_H repertoire and libraries by cloning cDNA from lymphoid cells (i.e., see page 8). The reference discloses that in the method of obtaining cDNA library composed of nucleotide sequences encoding heavy-chain immunoglobulins, a sample containing lymphoid cells, especially peripheral, lymphocytes, spleen cells, lymph nodes or another lymphoid tissue from a healthy animal, especially selected among camelids (refers to cloned from a non-immunized source' of the instant claim) (i.e., see the example in page 8). Thus, the reference clearly anticipates the claimed invention).

12. Applicant's arguments filed on 7/28/03 regarding the rejections of claims over either US Patent 5,800,988 (Casterman et al) or EP 584421 (Casterman) have been fully considered but they are not persuasive.

Applicants argue that Casterman et al does not disclose an expression library comprising repertoire of nucleic acids cloned from a non-immunized source. Applicants further argue that the reference in column 14, 'the preparation of antibodies without a previous immunization is not made in the context of anything resembling the applicant's invention.'

Applicants arguments have been considered and are not persuasive, since Casterman et al disclose immunoglobulins devoid of light chains. The reference discloses that the nucleic acid sequences of the disclosed immunoglobulins are used for the preparation of recombinant vectors and the expression of these sequences contained in the vectors by host cells (i.e., see column 11, lines 14-15). The reference discloses V_{HH} (variable heavy chain of immunoglobulin devoid of

light chain) repertoire (refers to the repertoire of nucleic acid sequences of the instant claims) using DNA derived from an arbitrarily chosen tissue or cell type or V_{HH} repertoire using DNA obtained from B lymphocytes. The reference discloses that the preparation of the antibodies can also be performed without a previous immunization of Camelids (see column 14, lines 15-16) (refers to the 'non-immunized source' of the instant claims).

The references clearly teaches that heavy chain antibodies naturally devoid of light chains can be prepared without a previous immunization of the camelids (i.e., see US Patent 5,880,988, column 12). Thus the reference clearly anticipates the claimed invention.

13. Claims 1-4 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ghahroudi et al (FEBS Letters, 414 (1997) 521-526).

The instant claims briefly recite an expression library comprising a repertoire of nucleic acid sequences, each nucleic acid sequence encoding a part of variable domain of a heavy chain derived from an immunoglobulin naturally devoid of light chains.

NOTE that the instant claims are considered as the product-by-process claims, in which the limitation 'cloned from a non-immunized source' is considered as process limitation.

Ghahroudi et al disclose single domain antibody fragments from camel heavy-chain antibodies (refers to instant claims 1 and 3) . The reference discloses that the functional heavy chain immunoglobulins lacking light chain (refers to 'naturally devoid of light chains' of the instant claims) occur naturally in Camelidae. The reference discloses cloning repertoire of variable domains of heavy chain antibodies (i.e., see the abstract). The reference discloses that V_{HH} library displayed on phage particles was generated by immunizing a camel. The reference discloses that libraries containing the variable region repertoire of heavy chains from immunized camel blood lymphocytes were constructed. The reference

discloses mRNA isolation from the lymphocytes and cDNA synthesis and cloning the CDR3 sequence (refers to 'at least a part of variable domain of heavy chain' of the instant claims) (i.e., see the materials and methods section).

The claimed invention differs from the prior art teachings by reciting 'cloned from non-immunized source'. However, the claimed expression library comprising repertoire of nucleic acid sequences encoding at least a part of a variable domain of a heavy chain naturally devoid of light chains, appear to be the same or obvious variations of the reference libraries, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to determine and/or compare the specific method of making the libraries of the instant versus the reference method which would result in patentably distinct compounds. . In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed library is structurally and functionally different rom the library of the reference which uses a different method to synthesize the library. See in re Best 562F.2d 1252, 195 U. S. P. Q. 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922(PTO Bd.Pat. App. & Int. 1989).

"The instant claims are written as product-by-process claims. "Even though the product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability is based on the product itself. The patentability of a product does hot depend on its method of production. If the product in the product-by-process claims is same or as obvious from the product of the prior art, the claim is unpatentable Even though the prior art product was made by a different process." In re Thorpe, 777 F. 2d 695, 698, 227 U. S. P. Q. 964, 966 (Fed. Cir. 1985). (see MPEP 2113).

14. Applicant's arguments filed on 7/28/03 regarding the rejection of claims over Gharoudi et al have been fully considered but they are not persuasive.

Applicants argue that Gharoudi et al does not disclose the applicants 'library or make it obvious. Applicants argue that Examiner can not disregard the applicants claim limitation

'cloned from a non-immunized source'. Applicants further argue that 'there are fundamental differences between nucleic acid sequences which are cloned from an immunized source and those cloned from non-immunized source. This is not a mere process limitation. This means that there is a high diversity within the claimed libraries.'

Applicants arguments have been fully considered and are not persuasive, since the instant claims recite 'an expression library comprising a repertoire of nucleic acid sequences cloned from a non-immunized source', in which 'cloned from non-immunized source' is considered as process limitation. The reference teaches cloning repertoire of heavy chain antibodies, and display of VH library on phage particles (expression vectors). Thus the reference teaches the product 'library of nucleic acid sequences encoding a variable heavy chain.' The reference does not teach the nucleic acid sequences (the product) are cloned from a non-immunized source which is considered as product-by -process limitation. Applicants argue that the instant library of antibodies have diversity. This is not persuasive, since the instant claims are drawn to a library (a product) and the reference discloses the library and the members of the reference library would read on the claimed library.

Further applicants argue that the applicants libraries are not enriched with one specific family of antibodies but contain the antibody variety that is not present in the immunized source.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., antibody which are not present in the immunized source or non-specific to one immunogen) are not

recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

"The instant claims are written as product-by-process claims. "Even though the product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability is based on the product itself. The patentability of a product does hot depend on its method of production. If the product in the product-by-process claims is same or as obvious from the product of the prior art, the claim is unpatentable Even though the prior art product was made by a different process." In re Thorpe, 777 F. 2d 695, 698, 227 U. S. P. Q. 964, 966 (Fed. Cir. 1985). (see MPEP 2113)."

Conclusion

15. No claims are allowed.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner is on ***Increased Flex Schedule*** and can normally be reached on Monday to Friday from 7.00 AM to 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

P. Ponnaluri
Patent Examiner
Technology Center 1600
Art Unit 1639
12 October 2003

PADMASHRI PONNALURI
PRIMARY EXAMINER